002181

Dicrotophos

Pesticide Registration Standard

April 1982

Office of Pesticides and Toxic Substances

Environmental Protection Agency

401 M Street, SW

Washington, D.C. 20460

1/85

002181

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Table III. A-3 Generic Data Requirements: Toxicology[1/] (See Chapter VI)

Guidelines Citation	Name of Test	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, when?
163.81-1	Acute Oral Toxicity	Technical Grade of Active Ingredient	partial [2/]	000013869	yes, 8 months
163.81-2	Acute Dermal Toxicity	Technical Grade of Active Ingredient	yes	000013869 000028521	no
163.81-3	Acute Inhalation Toxicity	Technical Grade of Active Ingredient	partial [3/]	000013443	yes, 14 months
163.81-4	Primary Eye Irritation	Technical Grade of Active Ingredient	yes	000013869	no
163.81-5	Primary Skin Irritation	Technical Grade of Active Ingredient	no	-	yes, 14 months
163.81-6	Dermal Sensitization	Technical Grade of Active Ingredient	no	-	yes, 14 months
163.81-7	Acute Delayed Neurotoxicity	Technical Grade of Active Ingredient	yes	000013444	no
163.82-1	Subchronic 90-Day Oral	Technical Grade of Active Ingredient	partial [4/]	000013564 000013869 000013441	yes, 14 months
163.82-2	Subchronic 21-Day Dermal Toxicity	Technical Grade of Active Ingredient	no	-	yes, 14 months

1/ Data requirements for Sections 163.81-1, 163.81-2, 163.81-3, 163.81-4, 163.81-5, 163.81-6 and 163.81-7 apply to all uses; data requirements for Sections 163.82-1, 163.82-2, 163.83-3, 163.83-4, 163.84-2 and 163.85-1 apply to ornamental (foliar application) and crop use (foliar application) only; and the remaining data requirements apply to crop use (foliar application) only.

2/ The rat study satisfies the requirement for males but a study in females rats is required.

3/ The rat study satisfies the requirement for males but a study in female rats is required. If the acute oral study indicates no difference in the toxicity to male and female rats, this requirement is satisfied.

4/ MRID# 00013441 is a valid study and will satisfy this requirement if an acceptable pathology report is provided. The other studies only partially satisfy the data requirement.

Dicamba

Table III. A-3 / Generic Data Requirements: Toxicology (see Chapter VI)

Guideline Citation	Name of Test	Composition	Does EPA Have Data to Partially or Totally Satisfy This Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, when?
163.83-1	Chronic Feeding	Technical Grade of Active Ingredient	no	-	delayed 1/
163.83-2	Oncogenicity	Technical Grade of Active Ingredient	no	-	delayed 1/
163.83-3	Teratogenicity	Technical Grade of Active Ingredient	partial 2/	GS0003501	yes 2/, 24 months
163.83-4	Reproduction	Technical Grade of Active Ingredient	no	-	delayed 1/
163.84-2	Mutagenicity	Technical Grade of Active Ingredient	yes	GS0003502 GS0003506	no
163.85-1	Metabolism	Analytical Grade	partial 3/	000013450	yes, 24 months

1/ The Agency is delaying a decision concerning these requirements pending the results of the following: residue chemistry data requirements on cottonseed, processed cotton seed, soybeans, and processed soybeans; and an applicator exposure study including data on applicator dermal and inhalation exposure. If these studies show no chronic exposure, the chronic toxicity studies will be waived; conversely, if the potential for chronic exposure is demonstrated, the studies will be required. Protocols for conducting the residue chemistry and applicator exposure studies must be submitted and approved by the Agency prior to their initiation and these studies must be completed within 12 months.

2/ The study is acceptable for rabbits but a study in rats is required.

3/ The rat study is acceptable for males but a study is required for female rats unless the acute oral study indicates no sexual difference in oral toxicity or the studies in footnote 1/ show no chronic exposure.

March, 1982

The acute oral toxicity of technical dicrotophos in various solvents has also been determined for CF_1 mice (Brown et al., 1964, 000013438). Sexes were combined in this study. The approximate LD_{50} of 2% dicrotophos (weight per volume, w/v in isopropyl alcohol) was 20 mg/kg and the approximate LD_{50} of 1% dicrotophos (w/v in dimethyl sulphoxide) was 40-50 mg/kg.

The acute oral toxicity of technical dicrotophos to rats (sex not specified) was reported by Witherup and Schlecht (1962, 000028521) as being 32.7 $\pm$ 2.5 mg/kg.

The acute dermal toxicity of technical dicrotophos in the rabbit was reported to be 224 (103-505) mg/kg (Schellenberger and Newell, 1962, 000013869) and 149 $\pm$ 18 mg/kg (Witherup and Schlecht, 1962, 00028521). The latter study satisfies that acute dermal toxicity data requirement.

The acute inhalation LC_{50} of technical dicrotophos in male Charles River CD rats was reported to be between 0.48 and 0.72 mg/liter (Witherup et al., 1965. 000013443); an inhalation toxicity study is required in female rats, however.

Technical dicrotophos was reported to be a very mild eye irritant in the rabbit (Shellenberger and Newell, 1962, 000013869). This study satisfies that primary eye irritation data requirement.

Single oral doses of technical dicrotophos up to an acute LD_{50} (7.4 + 0.7 mg/kg) did not produce signs of acute delayed neurotoxicity in hens (Witherup et al., 1963, 000013444). A single oral dose of 8 mg/kg technical dicrotophos (the LD_{50}) in atropine and protopam-protected hens produced no signs of acute delayed neurotoxicity. Lack of suitable control groups and insufficient information on histopathology, however, made proper evaluation of this study impossible (Boom and Forigan, 1965, 00014010).

In summary, technical dicrotophos has a high acute oral toxicity with LD_{50} values ranging from 12 to 30 mg/kg in the rat. The toxicity does not appear to be significantly affected by the solvent used. The acute dermal toxicity is also high, with an LD_{50} of 224 mg/kg reported in the rabbit. Also, a high acute inhalation toxicity, with an LC_{50} of between 0.48 and 0.72 mg/L, was reported in the rat. Dicrotophos does not produce organophosphate-type delayed neurotoxicity. Due to the high acute toxicity, this has been classified as a restricted use pesticide.

2. Subchronic Effects

In a 12-week feeding study of dicrotophos in young adult Long-Evans rats, the only effect reported was depression of weight gain at a dietary level of 135 ppm both sexes and 45 ppm females. A no-observable-effect level (NOEL) of 15 ppm was established. Insufficient animals were used, however, and they were not weanlings; the study is therefore classified as supplementary (Shellenberger and Newell, 1962, 000013869).

Also, weanling Long-Evans rats were studied for the effect of dicrotophos on whole blood and brain cholinesterase. For both sexes whole blood

cholinesterase was depressed at dietary levels of 4.5 and 1.5 ppm but not at 0.5 ppm in both sexes. There was a statistically significant depression of brain cholinesterase at the 4.5 ppm dose level. There was a similar depression, although not statistically significant, at the 1.5 ppm dose level and no effet at the 0.5 ppm dose level. Whole blood activity returned to normal within two weeks and brain activity within three weeks after cessation of treatment. A NOEL for depression of brain and whole blood cholinesterase activity was established at 0.5 ppm. Various deficiencies required the classification of this study as supplementary (Shellenberger and Newell, 1962, 000013869). In the subchronic testing in rats, the major toxic effects were depression of weight gain and depression of cholinesterase activity.

A 13-week feeding study of dicrotophos in young beagle dogs at dietary levels of 1, 5, and 50 ppm showed depression in red blood cell (RBC) and brain (50 ppm) cholinesterase activity. These effects occurred only at the 50 ppm dose level and were the only signs of toxicity. This study is considered supplementary because the pathologist's report was not included (Witherup et al., 1964, 000013441).

A 2-year feeding study of dicrotophos in beagle dogs at 0.16, 16, and 100 ppm revealed signs of toxic effects at 100 ppm (salivation, soft stools, and/or tremors) (Johnson et al., 1967, 000013564). Significant decreases in plasma and RBC cholinesterase were observed at 16 and 100 ppm but not at 1.6 or 0.16 ppm. A NOEL of 1.6 ppm was established for depression of plasma and RBC cholinesterase activity. Damage to the pyloric region of the stomach was observed in 2 of 3 females at 100 ppm. The high dose animals were only treated for one year. Insufficient animals were tested and the study was classified as supplementary.

A subchronic 21-day dermal toxicity study included application of technical dicrotophos to the skin of rabbits at doses of 20 and 40 mg/kg/day for 21 days (Doyle and Elson, 1965, 00005117). No compound-related toxicity was observed. The study is classified as supplementary because these doses produced no effect and a maximum dose of 2000 mg/kg was technically feasible to apply.

Five consecutive daily oral doses of technical dicrotophos given to hens at 2.4 mg/kg/day produced no neurotoxic effect during a 21 day observation period (Brown & Ferrigan, 1965, 000014010). This study is classified as supplementary because, the dose was not administered for the required period.

A subchronic neurotoxicity study which included repeated dosing of 15 hens with technical dicrotophos at daily doses of 1.5 mg/kg/day twice during the first week and 0.75 mg/kg/day five times per week during the second and third weeks (Witherup et al., 1963 000013444). No signs of delayed neurotoxicity were produced. These studies failed to demonstrate organophosphate-type delayed neurotoxicity and are classified as supplementary because the dose was not administered for the required period. Testing is not required since the acute neurotoxicity test was negative.

3. Chronic Effects

In a 2-year feeding study, dicrotophos caused excessive mortality, compared to controls, in male rats at all doses (1, 10, and 100 ppm) and in female rats at 10 and 100 ppm (Johnson, 1966, 000013966 and Howard et al., 1967, 000013563). Plasma cholinesterase was depressed at all doses in both sexes and RBC cholinesterase at 10 and 1,000 ppm in both sexes. Growth was depressed at 100 ppm in both sexes. The study does not satisfy Agency requirements since it lacked sufficient animals at the start, surival was less than 20 percent in most treated groups, and a NOEL was not demonstrated.

Oral teratogenicity studies were performed in Dutch Belted rabbits (Dix, Wilson, et al., 1973, GS0003501) Technical dicrotophos was administered on days 6-18 of pregnancy at doses of 1.3, 4, or 8 mg/kg/day. Thalidomide, at doses of 37.5 or 75 mg/kg/day, was used as a positive control. Although, maternal toxicity including signs of cholinesterase inhibition, was observed at 8 mg/kg/day, no fetal toxicity attributable to dicrotophos was observed at this dose. Teratogenicity was demonstrated at the maximum thalidomide dose of 75 mg/kg/day.

Young adult rats fed dicrotophos at 0.3, 3.0, and 30 ppm for up to 25 weeks showed no toxic effects (Witherup et al., 1964, 000013445). Breeding and fertility were normal in the two matings per animal. No gross teratogenic effects were observed. Survival of offspring at 30 ppm was severely affected, with 80 percent mortality for the first mating and 93 percent mortality for the second mating during the first week.

Dicrotophos at 50 ppm in the diet of pregnant rats caused an increase in the number of embryos absorbed (9.7% vs 1.14% in controls) at the 17th day of pregnancy (Bulter, 1965, 000013447). At 100 ppm there was a 26.5% reduction of conceptuses. No gross abnormalities were observed in the surviving fetuses and no maternal toxicity was observed.

The above rat studies do not satisfy the Guideline's requirements for teratology testing since they lack necropsy and histopathological examination of the fetuses.

In a 3-generation reproduction study, dicrotophos produced toxic effects on fetuses at 5, 15, and 50 ppm (Eisenland and Logwan 1965, 000013446). No toxic effect was observed at 2 ppm. Insufficient litters were produced, individual litter data were not reported, and the histopathology was only summarized, not reported in detail. Consequently, the study does not satisfy Guidelines requirements for reproduction studies

4. Mutagenicity

An in vivo study on induction of chromosomal abberrations was performed in CF_3 mice (Snell, 1973, GS0003502). Analytical grade dicrotophos was administered orally in a single oral dose of 5 or 10 mg/kg. The animals were

killed after 8 or 24 hours, and chromosomal preparations were made from bone marrow cells. The incidence of chromosome abnormalities did not differ from that in controls.

A dominent lethal assay of technical dicrotophos was performed in male mice of the CFI strain (Shell, 1974, GS0003506). Single oral doses of 5 or 10 mg/kg or 5 consecutive oral doses of 1 or 2 mg/kg/day were tested. The males were then mated weekly with three female mice per week for eight weeks after dosing. Methyl methonesulphonate, 1 mg/kg I.P. was used as a positive control. Dicrotophos treatment did not effect pregency or result in detectable dominant lethal mutations in comparison with the untreated controls.

Four different mutagenic studies with technical dicrotophos were reported (Shell, 1974, GS0003506):

1. A host mediated assay was conducted with Saccaromyces cerevisiise D4[4] in male CFI mice. At single oral doses of 5 or 10 mg/kg, no mutagenic effect was observed.

2. An in vitro study was conducted with Saccaromyces cerevisiae D4[4]. No mutagenic effects were observed at concentrations of 30 micrograms/ml, 5 mg/ml, 20 mg/ml or 50 mg/ml.

3. An in vitro test with Serratin marcescenes, Hy a 13, Hy a 21[6] and CV/VC3 742[7]. No dose data was given. It was reported that this study was negative.

4. An in vitro test with Samonella typhimurium TA1536, TA1537 and TA1538, was conducted. No dose data was reported. It was reported that the study was negative.

The two studies together satisfy the mutagenicity data requirement.

5. Metabolism

In the male rat, dicrotophos rapidly excreted in the urine mainly as the dimethyl and other hydropholic phosphides and the de-N-methylated dicrotophos. (Poonawalla, 1965, 000013450). The compound and its metabolites did not accumulate in tissue and no bioaccumulation occurs. Metabolism studies are needed in female rats.

6. Antidotal Studies

Studies with young adult female rats showed that treatment with a combination of atropine sulfate and the oxine Toxogonin was most effective in decreasing the acute toxic effect of oral dicrotophos (Reiff, 1968, 000013569).

B. Human and Domestic Animal Hazard Assessment

Technical dicrotophos has a high acute oral and acute dermal toxicity. The acute toxicity of dicrotophos falls in Category I for oral LD_{50} and dermal LD_{50}; in Category II for inhalation LD_{50}; and in Category III for eye

effects. The Agency believes that the acute hazards are mitigated by the precautionary measures prescribed by product labeling and restricted to use by certified applicators.

The Agency's Pesticide Incident Monitoring System (PIMS, 1981) reported 31 incidents involving dicrotophos during the period 1966 to July, 1981. Twenty two incidents involved dicrotophos alone. The other nine incidents involved dicrotophos in combination with other ingredients. Humans were involved in 13 incidents in which dicrotophos alone was cited as causing the alleged adverse effects. Three of the 13 incidents involved home use of dicrotophos for which dicrotophos is not currently registered. The home related incidents were clearly a misuse since the user disregarded the label instructions. All but one of the remaining ten incidents involved noncertified applicators and were attributed to accidental spills or were of undetermined origin. Seven of the ten incidents involved dermal exposure, two involved eye exposure and one was unknown. Toxic effects included nausea, vomiting, abdominal cramps, troubled breathing, weakness and cramps. No deaths were reported and atropine was administered in five of the incidents to assist in recovery. The one incident involving a certified applicator, occurred as a result of a plane crash during aerial application.

The information available to assess potential hazard as a result of chronic exposure is incomplete (see Chapter III for detailed data requirements). The Agency has an acceptable teratology study in rabbits, which indicated no fetal toxicity or gross teratogenic effects at the dose levels tested. However, an unacceptable chronic feeding study indicated excessive mortality and cholinesterase depression. An unacceptable reproduction study indicated fetotoxic effects at the higher dose levels. The unacceptable studies provide onlysupplementary data and cannot be used to draw conclusions concerning margins of safety.

Data are not available to fully assess the potential for exposure of humans to dicrotophos. Applicator inhalation exposure is possible through foliar application to cotton and soybeans grown for seed and mixing and loading operations. Dermal exposure is possible; but should be mitigated with the labeling requirements for protective clothing. Exposure associated with the injection use of dicrotophos on ornamental trees should be negligible since both the injection unit and the sites (trees) are closed systems. Dietary exposure is possible through dicrotophos residues in cotton and soybean food products. Additional food residue information is being required to support continued use on cotton, and seed soybeans (see Chapter III). The registrant may conduct residue chemistry and applicator exposure studies to determine if there is any human chronic exposure to dicrotophos. If these studies demonstrate that there is no human chronic exposure, chronic toxicity studies will not be required. Conversely, if the potential for chronic exposure is demonstrated the chronic toxicity studies will be required (reference Table III. A-3).

C. Summary of Data Gaps

The following generic data are required: acute oral toxicity in female rats, primary skin irritation, dermal sensitization, subchronic 21-day dermal

toxicity at nigher doses, teratogenicity in rats, and mutagenicity. An acute inhalation toxicity study and a metabolism study in female rats is required unless the acute oral toxicity study in female rats indicates no sexual difference in oral toxicity. A subchronic 90-day oral study is required unless an acceptable pathology report is provided for Witherup et. al. (1964, 000013441). Chronic feeding, oncogenicity, and reproduction data requirements are reserved pending the results of residue chemistry data requirements on cottonseed, processed cotton seed, soybeans, and proccessed soybeans. These chronic studies will be required if dicrotophos residues appear in these food products.

Additional product specific data will not be required if the severest labeling restriction (i.e., the signal word "DANGER" and a skull and crossbones) appears on the product label.

MRID 00013966

00013564

Chemical - Bidrin

Type of Formulation - Technical

Citation

Johnston, C.D. (1966) Bidrin: Safety Evaluation by Chronic Feeding: Studies in the Rat and the Dog for Two Years: Interim Report: 52 Weeks. (Unpublished study received Dec. 2, 1966, under 7G0571; prepared by Woodard Research Corp., submitted by Shell Chemical Co., Washington, D.C.; CDL:090721-A).

NOTE - Only that portion of the above report relating to the DOG study will be presented in this DER.

Jonnston, C.D.; Thompson, W.M.: Donoso, J. (1967) Bidrin Safety Evaluation by a Chronic Feeding Study in the Dog for Two Years: Final Report. (Unpublished study received June 2, 1971, under 1F1062; prepared by Woodward Research Corp., submitted by Shell Chemical C., Washington, D.C.; CDL:091826-B).

Reviewed by - Robert P. Zendzian, Ph.D. 11/9/81

Conclusion:

Signs of compound related toxicity were observed at 100 ppm (salivation, soft stools and/or tremors). Significant decreases in plasma and RBC cholinesterase

were observed at doses of 16 and 100 ppm. No compound related effects were observed at 1.6 or 0.16 ppm. The pylorus was adversely affected in 2 of the 3 100 ppm females.

Core Classification - Supplementary

Materials and Methods

Technical Bidrin, a light brown liquid with a concentration of "90 lbs per gallon" was used in this study. Bidrin was administered in the diet. Twenty-six beagle dogs (13 M and 13 F) six to eight months of age were assigned to four treatment groups.

Group	1	4M	4 F	Control
	2	3M	3 F	16 ppm
	3	3M	3 F	1.6 ppm
	4	3M	3 F	0.16 ppm

After 52 weeks of study, an additional 2M and 2F were assigned to a 100 ppm group.

Body weight and general condition of each dog were determined weekly. Electrocardiograms and blood pressures were run at 0, 6, 13, 26, 39, 52, 84, 95 and 104 weeks (Groups I-IV), and at 0, 6, 13, 26, 39 and 52 weeks for Group V. An opthalmic examination was made on each dog at 0, 6, 13, 26, 39, 52, 78 and 104 weeks (Groups I-IV) or 0, 6, 13, 26, 39 and 58 weeks (Group V). Hemograms, consisting of hemoglobin and hematocrit determinations,

sedimentation rates, thrombocyte counts, and total and differential white cell counts, were run on all beagles in Groups I-IV at 0, 6, 14, 18, 26, 40, 53, 78, 93 and 104 weeks and at 0, 6, 13, 19, 26, 40 and 52 weeks for Group V.

Clinical chemistry determinations of blood urea nitrogen, blood glucose, serum alkaline phosphatase, serum glutamic-pyruvic and glutamic-oxalacetic transaminases, plus plasma and erythrocyte (RBC) cholinesterase activities, were also done at the same intervals in the respective groups of beagles. Qualitative urinalyses were done at nearly the same intervals. At termination, surviving animals in each group were sacrificed by exsanguination under sodium pentobarbatal anesthesia and a gross autopsy was performed on each.

Reported

One female dog in the 100 ppm group was sacrificed "at point of death." Necropsy indicated ulceration of pyloric region of stomach with dark tarry material in the digestive tract. The second female 100 ppm showed pyloric portion of stomach with thick walls and a red raised area in the upper portion of duodenum at terminal sacrifice.

There were some instances of slight salivation in dogs given 16, 1.6 and 0.16 ppm of Bidrin and slight fairly consistent salivation, soft stools and/or tremors in the 100 ppm Beagles.

Significant decreases in plasma and RBC cholinesterase were reported in both sexes at 16 and 100 ppm. Brain cholinesterase values at 100 ppm were depressed in both males when first assayed but only in one male on a repeat

MIRD 00013966

00013563

Compound - Bidrin

Type of Formulation - Technical

Citation

Johnson, C.D. (1966) Bidrin: Safety Evaluation by Chronic Feeding: Studies in the Rat and Dog for Two Years: Interim Report: 52 Weeks. (unpublished study received Dec. 2, 1966 under 7G0571; prepared by Woodard Research Corp., submitted by Shell Chemical Co., Washington, D.C.; CDL:090721-A).

NOTE - This DER only covers that part of the report pertaining to the RAT study.

Howard, D.J.; Dunoso, J.; Johnson, C.D. (1967) Bidrin Safety Evaluation by a Chronic Feeding Study in the Rat for Two Years: Final Report. (Unpublished study received June 2, 1971 under 1F1062; prepared by Woodard Research Corp., submitted by Shell Chemical Co., Washington, D.C.; CDL:091826-A).

Reviewed By - Robert P. Zendzian, Ph.D. 8/17/81

Topic - This study has information pertaining to the discipline toxicology, topic chronic oral toxicity. It pertains to the proposed Guideline Data Requirements 163.83-1 and 163.83-2.

Conclusion - Bidrin in the diet caused excessive mortality in male rats at 1, 10, and 100 ppm and in female rats at 10 and 100 ppm. Plasma cholinesterase was depressed at all doses and RBC cholinesterase at 10 and 100 ppm. Growth and food consumption were depressed at 100 ppm.

Core classification - Supplementary

Materials and Methods

Technical Bidrin, a light brown liquid with a concentration of "9.0 lbs per gallon" was used in this study. Bidrin was administered in the diet.

230 weanling Charles River rats were assigned to the following treatment groups.

I	40 males 40 females	controls
II	25 males 25 females	100 ppm
III	25 males 25 females	10 ppm
IV	25 males 25 females	1 ppm

Animals were observed daily and body weight and food consumption recorded weekly. Hemaglobin, hematocrit and WBC counts, total and differential, were obtained at 6, 13, 19, 26, 39, 52, 78, 91, and 104 weeks on five male and five female rats from the control and the 100 ppm groups.

Plasma and RBC cholinesterase activity was determined at 6, 13, 26, 52, 78 and 104 weeks from five males and five females in each treated group and for 10 male and 10 female controls.

Rats that died in study or were sacrificed for cause were necropsied. Tissues were collected where possible.

Survivors at 104 weeks were sacrificed and necropsied. Organs weighed and tissues taken are shown in the table.

	Organ Weighed	Examined Microscopically			
			Bidrin		
Tissue	All Fats	Control	100 ppm	10 ppm	1 ppm
Liver	x	x	x	x	x
Kidneys	x	x	x	x	x
Heart	x	x	x		
Lungs	x	x	x	x	x
Spleen	x	x	x		
Gonads	x	x	x	x	x
Adrenals	x	x	x	x	x
Thyroid	x	x	x	x	x
Pituitary	x	x	x	x	x
Prostrate/Uterus	x	x	x		
Brain	x	x	x		
Duodenum	x	x	x		
Muscle, intercostal		x	x		
Urinary bladder		x	x		
Pancreas		x	x		
Lymph node, mesenteric		x	x		
Bone marrow		x	x	x	x
Stomach		x	x		
Spinal cord		x	x		
Tissue Mass		x	x	x	x
Eye		x	x		

One brain hemisphere from each of at least 56 percent of the survivors of each sex per group was analyzed for cholinesterase activity.

Mortality during the study is summarized as follows:

Weeks	Control		Bidrin 100 ppm		Bidrin 10 ppm		Bidrin 1 ppm	
	M	F	M	F	M	F	M	F
1-52	2		4	1	2		1	
53-65	3		1	1	1	2	1	
66-78	9	2	11	4	11	6	16	2
79-91	3	5	2	4	4	5	1	3
92-104	6	2	2	6	2	2	3	2
Total	23	9	21	16	20	15	22	7

Males and females at 100 ppm weighed 66 and 85 percent of control weights at 104 weeks. Growth was retarded throughout most of the study. Food consumption was depressed at 100 ppm.

Blood Cholinesterase activity is summarized below:

Diet Level ppm	Mean Cholinesterase Activity ΔpH/Hour weeks 6	13	26	52	78	104	Mean	% Contol
				Males-Plasma				
Control	0.29	0.43	0.26	0.63	0.49	0.57	0.45	100
100	0.19	0.05	0.02	0.14	0.10	0.28	0.13	19
10	0.22	0.12	0.04	0.25	0.22	0.37*	0.50	44
1	0.22	0.40	0.24	0.47	0.39	0.36	0.35	78
				Females-Plasma				
Control	0.78	1.19	1.01	1.25	1.15	1.07	1.08	100
100	0.14	0.08	0.01	0.10	0.08	0.35	0.13	12
10	0.21	0.23	0.16	0.44	0.32	0.39*	0.27	27
1	0.66	0.81	0.71	1.01	0.76	0.64	0.77	71
				Males-RBC				
Control	0.48	0.53	0.43	0.57	0.57	0.47	0.51	100
100	0.09	0.01	0.12	0.01	0.11	0.22	0.08	16
10	0.24	0.09	0.11	0.37	0.46	0.35*	0.27	53
1	0.52	0.38	0.35	0.48	0.63	0.37	0.47	92
				Females-RBC				
Control	0.57	0.58	0.46	0.71	0.69	0.49	0.58	100
100	0.07	0.02	0.00	0.00	0.04	0.36	0.08	14
10	0.31	0.16	0.12	0.20	0.29	0.22*	0.22	38
1	0.61	0.39	0.38	0.57	0.60	0.41	0.49	83

Mean Brain Cholinesterase values were as follows:

Diet Level ppm	Sex	Mean Δ pH/Hour Sacrificed	Mean Δ pH/Hour Died on Test
Control	Male	0.74	0.84
	Female	0.84	0.90
100	Male	0.09	0.24
	Female	0.32	0.22
10	Male	0.48	0.58
	Female	0.74	0.62
1	Male	0.60	0.86
	Female	0.81	1.00

A lower frequency of hepatocellular inoculations in rats given Bidrin 100 ppm than in the other groups was the only reported histopathological change that may have been compound related.

Discussion

The study is not sufficient to evaluate the chronic toxicity of Bidrin in rats. Excessive mortality occurred in the treated males. Over 50% mortality had occurred by 18 months on test and final mortality was 84%, 80% and 88% treated compound with 58% in controls. In the females, excessive mortality occurred in the 100 ppm (64%) and 10 ppm (60%) compared with the 1 ppm (28%) and controls (23%).

Due to the small number of animals on test, at 25 only half the recommended number, the number surviving in these groups ranged from 10 to 3. These numbers are too small to evaluate chronic toxicity.

Depression of plasma cholinesterase (mean values for the entire study as % of control) was observed at all doses in both sexes, however the depression at 1 ppm was at the borderline of significance. Depression of RBC cholinesterase (mean values for the entire study as % of control) was observed at 100 and 10 ppm in both sexes.

MIRD 00013446

Chemical: Bidrin

Type of Formulation: Not stated, probably technical.

002181

Citation:

Eisenlord, G.; Loquram, G.S. (1965) Results of Reproduction Study of Rats Fed Diets Containing Bidrin Insecticide Over Three Generations: Report No. 3. (Unpublished study received January 28, 1966 under 201-142; prepared by Hine Laboratories, submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-L).

Reviewed by Robert P Zendzian Ph D 12/16/81

Topic: This study has information pertinent to the discipline toxicology, topic reproduction. It relates to the proposed data requirements 163.834.

Conclusion:

Bidrin produced toxic effects on fetuses at 5, 15 and 50 ppm in the diet. No toxic effect was observed at 2 ppm.

Core Classification: Supplementary

Materials and Methods:

Bidrin was disolved in water and mixed with powdered maintenance rat food to produce food concentrations of 2, 5, 15 and 50 ppm. The formulation of Bidrin was not stated but was probably technical. The study was conducted in two parts. In part one, weanling Long-Evans rats were assigned, ten males and twenty females, to groups receiving 0, 5, 15 or 50 ppm Bidrin. The rats were mated at 100 days of age. The F_{1a} litters were sacrificed and dissected at weaning and the F_o animals mated after ten days. Pups were selected from the F_1b litters, maintained on the diet until 100 days old and mated to produce F_2a and then F_2b litters. Rats from the F_2a litters were used to produce the F_3a litters. Due to excussive mortality in the 50 ppm group an additional group was treated. In part two, weanling Long-Evans rats were assigned, ten males and twenty females, to groups receiving 0 and 2 ppm Bidrin.

Each generation in part two was mated only once F_0 to F_1a to F_2a to F_3a. In both parts the final litters were preserved for histological examination. Parent rats were weighed, sacrificed and examined grossly, when no longer needed 10 males and 10 female F_3a weanlings from the control groups and 15 ppm group and 5 males and 5 females each from 2 ppm and 5 ppm groups were selected for necropsy. Individual body weights and brain, liver and kidney weights were recorded. Sections of brain, heart, lung, liver, spleen, pancreas, kidney and testes were preserved for histological examination.

Reported:

No toxic signs were observed in the animals receiving 2, 5 or 15 ppm Bidrin in the diet. At 50 ppm signs of toxicity were observed. High mortality occurred in the litters so that this dose group could not be continued. Summary data generated in this study were presented in Tables 1 through 4 from the reports. Toxic effects on reproduction was observed at 5, 15 and 50 ppm but not at 2 ppm. Histopathological examination of tissues from F_3a weanlings showed "questionable" lung changes at 5 and 15 ppm but no effects at 2 ppm.

Discussion:

The data reported is not sufficient to properly evaluate the study. Insufficient litters were produced, individual litter data is lacking and the histopathology is summarized but not reported.

Table 1: Numbers and Weights of Litters in Three-Generation Bidrin Study

Generation	Group (ppm)	No. of Litters	Average No. per Litter	Average No. per Litter 5th Day	Average No. per Litter 21st Day (a)	Average Wt. of Surviving Pups (gm)	No. of Litters Not Surviving
F_1a	Control	20/20	9.0	9.0	8.6	37.6	0/20
	5	18/20	10.1*	9.8	9.3	35.7	0/18
	15	19/20	7.5	6.7	6.6	33.8	0/19
	50	14/20	8.4	6.9	6.2	29.5	4/14
F_1b	Control	20/20	10.0	9.9	8.3	31.4	0/20
	5	18/20	11.2	11.1	8.6	33.7	1/18
	15	19/20	9.5	8.7	7.6	32.2	1/19
	50	16/20	5.7**	5.0	5.0	30.5	10/16
F_2a (from F_1b)	Control	20/20	9.8	9.5	7.9	37.0	0/20
	5	20/20	9.8	9.2	5.8	36.0	2/20
	15	19/20	8.8	8.4	5.1	33.7	4/19
2b	Control	18/19	9.7	9.3	6.7	39.1	0/18
	5	19/20	9.8	8.9	5.6	35.1	1/19
	15	16/20	8.9	3.3	4.8	37.1	2/16
F_3a (from F_2a)	Control	18/20	9.3	8.8	7.5	36.0	1/18
	5	17/20	7.8	7.6	6.8	35.8	0/17
	15	19/20	8.7	8.6	6.3	34.6	2/19
F_1a	Control	20/20	7.8	7.7	7.4	38.9	0/20
	2	19/19	9.2*	9.2	8.7	33.6	0/19
F_2a	Control	18/20	9.7	9.6	8.6	32.8	0/18
	2	20/20	10.0	9.0	7.3	37.4	1/20
F_3a	Control	20/20	10.2	9.5	8.5	34.1	2/20
	2	16/20	9.4	9.1	6.9	36.5	2/16

(a) Excluding litters in which all pups died.
* Significant for 95% probability
** Significant for 99% probability

Table 2: Numbers of Pups Born and Their Percent Mortality

Generation	Group (ppm)	Total Pups Born (a)	Total Pups Weaned	% Mortality
F_1a	Control	172	172	0
	5	170	167	1.8
	15	142	125	12.0*
	50	115	62	46.1**
F_1b	Control	181	175	3.3
	5	172	147	14.5
	15	169	135	20.1*
	50	89	30	66.3**
F_2a	Control	182	157	13.7
	5	185	105	43.2**
	15	164	76	53.7**
F_2b	Control	159	120	24.5
	5	173	100	42.2**
	15	129	67	48.1*
F_3a	Control	161	130	19.3
	5	132	115	12.9
	15	162	107	34.0
F_1a	Control	153	148	3.3
	2	170	165	2.9
F_2a	Control	168	155	7.7
	2	179	139	22.3
F_3a	Control	190	153	19.5
	2	139	96	30.9

(a) Excluding pups sacrificed on 5th day to reduce litter size to 10.
* Significant for 95% probability
** Significant for 99% probability

Table 3: Terminal Weights of Parent Rats

Generation	Sex	Average Weights in Grams		
		Control	5 ppm	15 ppm
F_1b	Males	473	469	420
	Females	311	304	305
F_2a	Males	411	401	417
	Females	289	264	268
F_1a	Males	399	442	
	Females	278	312	
F_2a	Males	430	445	
	Females	293	312	

Table 4: Average Organ Weights and Organ-Body Weight Ratios[a] of F_{3a} Weanlings

Sex	Group (ppm)	Body Wt (gm)	Brain Wt (gm)	Brain Ratio	Liver Wt (gm)	Liver Ratio	Kidneys Wt (gm)	Kidneys Ratio
Males	Control	36	1.21	3.44	1.50	4.13	0.43	1.20
	5	36	1.25	3.57	1.51	4.17	0.47	1.30
	15	34	1.23	3.66	1.48	4.32	0.44	1.28
	Control	35	1.28	3.72	1.47	4.25	0.42	1.22
	2	37	1.22	3.30	1.53	4.15	0.45	1.22
Females	Control	32	1.18	3.67	1.36	4.22	0.40	1.26
	5	33	1.21	3.71	1.49	4.59	0.45	1.38
	15	34	1.17	3.52	1.52	4.56	0.44	1.30
	Control	33	1.24	3.36	1.56	4.34	0.43	1.30
	2	36	1.21	3.36	1.55	4.28	0.46	1.28

(a) $\frac{\text{Organ Wt}}{\text{Body Wt}} \times 100$

MRID 00013447

Chemical - Bidrin

Type of Formulation - Not specifically stated, probably technical.

Citation

Butler, H. (1965) A Preliminary Investigation into the Effect of Bidrin on Reproduction in the White Rat. (Unpublished study received Jan 28, 1966 under 201-142; prepared by Univ. of Saskatchewan, Dept. of Anatomy, submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-5)

Reviewed by - Robert P. Zendzian, Ph.D. 11/14/81

Review Section #3

Toxicology Branch/HED (TS-769)

Topic - This study has information pertinent to the discipline toxicology, topic teratology. It relates to the proposed Guidelines 163.83-3 data requirements.

Conclusion

Bidrin, at 50 ppm in the diet of pregnant rats caused an increase of absorption of embryos (9.7% vs 1.14% controls) at the 17th day of pregnancy. At 100 ppm there was a 26.5% reduction of conceptases. No gross abnormalities were observed in the fetuses. No maternal toxicity was observed.

Core Classification - Supplementary

Materials and Methods

The test material was not characterized but was probably technical Bidrin. The material was dissolved in water and mixed with the diet to give final concentrations of 50 and 100 ppm. Nine females were fed 50 ppm starting three weeks before breeding until the 17th day of pregnancy when the animals were killed. The uteri were examined and the number of implantation sites and fetuses counted. The fetuses were examined for gross abnormalities at 100 ppm Twelve females were treated in a similar manner except that they were killed at 10 or 11 days of pregnancy. An equal number of control animals were carried for each dose.

Reported

At 50 ppm of Bidrin in the diet no maternal toxicity was reported. In the treated females 9.7% of the total conceptases were resorbed compared with 1.7% in the contrcls. No gross fetal abnormalities were reported. At 100 ppm no maternal toxicity was reported. Implantation was reduced 26.3% compared with the controls. No gross fetal abnormalities were reported.

Discussion

This study is a preliminary teratology study and is sufficient to provide the basis for a complete study. The study lacks sufficient animals per doses, a NOEL dose, and histopathological examination of the fetuses.

MRID 00013445

002181

Chemical - Bidrin

Type of Formulation - Technical (80%)

Citation

Witherup, S.; Stemmer, K.L.; Schlecht, H. (1964) The Effects of the Regular Ingestion of Bidrin Insecticide-(R) in the Diet Upon Fertility of Rats and the Viability of their Offspring. (Unpublished study received Jan 28, 1966 under 201-142: prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-K)

Reviewed by - Robert P. Zendzian, Ph.D. Pharmacologist 12/14/81

Topic - This study has information pertaining to the discipline toxicology, toxic teratology. It relates to the proposed Guideline Data Requirements 163.83-3.

Conclusions

Young adult male and female rats fed Bidrin at concentrations of 0.0, 0.3, 3.0 and 30.0 ppm for periods of up to 25 weeks showed no toxic effects. Breeding and fertility were normal at all doses. No gross teratogenic effects were

observed. Survival of offspring at 30.0 ppm was severely affected, 80 and 93 percent mortality during the first week.

Core Classification - Supplementary

Materials and Methods:

The test material was technical bidrin (80% by weight 3-(dimethexy phosphiny loxy)-N, N-cis-corotonamide. The material was a dark brown liquid (s.g. 1.22) soluble in water, acetone, ethanol and xylene. The material was mixed with the feed, Purina Laboratory Chow, at concentrations of 0.0, 0.3, 3.0 and 30.0 ppm. Young adult rats were accumulated for one week and then assigned to the following groups: Control, 5 males and 10 females; and three treatment groups of 10 males and 20 females each. After the animals had been fed their respective diet for two weeks they were housed, one male and two females, in the same treatment group, until pregnancy was observed.

Shortly after birth each pup was weighed and observed for abnormalities. Pups from the first litter were killed at 7 days and subjected to gross necropsy. The second litters and dams were killed at three weeks and necropsied. No histopathology was performed.

Reported:

The results of this study was summarized in the tables below taken from the report.

TABLE 1
DEATH ADULTS

Concentration of Bidrin (ppm)	MALES		FEMALES	
	Number of deaths	Weeks of feeding at time of death	Number of deaths	Weeks of feeding at time of death
0.0	1	10	1	10
0.3	1	10	1	15
3.0	0	--	0	--
30.0	0	--	1	17

TABLE 2
FERTILITY OF FEMALES

Concentration of Bidrin (ppm)	First litters			Second litters		
	Number of females put to test	Number of litters delivered alive	Percentage of fertile females	Number of females put to test	Number of litters delivered alive	Percentage of fertile females
0.0	10	10	100	0	7	78
0.3	20	18	90	18	15	83
3.0	20	18	90	18	14	78
30.0	20	16	80	15	10	67

TABLE 3
FERTILITY OF MALES

Concentration of Bidrin (ppm)	Number of males put to test	Males that sired progeny	
		Number	Percent
0.0	5	4	80
0.3	10	10	100
3.0	10	10	100
30.0	10	9	90

TABLE 4
LITTERS AND PUPS

Concentration of Bidrin fed to the progenitors (ppm)	First Mating			Second Mating		
	Number of Litters	Total number	Number of pups	Number of litters	Total number of pups	Number of pups per 10 litters
0.0	10	99	99	7	74	106
0.3	18	195	108	15	173	115
3.0	18	174	97	14	161	115
30.0	16	135	84	10	98	98
Total	62	603	97*	46	506	110*

* Average

TABLE 5
MORTALITY OF PUPS

Concentration of Bidrin fed to the progenitors (ppm)	First Mating			
	Number of pups born	Number of deaths		Mortality (percent)
		at birth	during 1 week	
0.0	99	0	29	29
0.3	195	10	80	46
3.0	174	2	43	26
30.0	135	20	88	80
		Second mating		
0.0	74	3	35	51
0.3	173	3	96	57
3.0	161	2	61	39
30.0	98	12	79	93

TABLE 6
WEIGHT OF PUPS AT BIRTH

Concentration of Bidrin fed to the dams (ppm)	First Litters		Second Litters	
	Males (g.)	Females (g.)	Males (g.)	Females (g.)
0.0	6.0	5.9	5.9	5.6
0.3	6.6	6.3	6.5	5.9
3.0	6.4	6.1	6.1	5.6
30.0	6.0	5.8	5.8	5.2

TABLE 7
WEIGHT OF PUPS AT THREE WEEKS

Corcentraton of Bidrin fed to the dams (ppm)	Males		Females	
	Number weaned	Average bodily weight (g.)	Number weaned	Average Bodily weight (g.)
0.0	16	39	20	35
0.3	30	47	29	41
3.0	54	41	44	37
30.0	1	47	6	45

No gross terata were observed in any pups of any group, control or treatment.

Discussion:

This study is considered supplementary in that it provides a basis for dose selection for a rat teratology study. However the study utilized only half the number of females (and litters) required, the offspring were ~~out~~ not delivered by Cesarean and no histopathology was performed.

MIRD 00013441

Chemical - Birdrin

Type of Formulation - Technical

Citation

Witherup, S.; Stemmer, K.L.; Caldwell, J.S., Jr. (1964) The Effects upon Dogs of the Regular Ingestion of Bidrin Insecticide (R) in Their Diet.

(Unpublished study received Jan. 28, 1966 under 201-142; prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, D.C.: CCDL:000834-G)

12/9/81

Reviewed By - Robert P. Zendzian, Ph.D.

Topic

This study has information pertinent to the discipline toxicology; topic subchronic oral toxicity. It relates to the proposed Guideline data requirements 163.82-1.

Conclusion

Young beagle dogs, of both sexes, fed Bidrin in the diet of 1, 5 and 50 ppm for 12 weeks showed plasma (1, 5 & 50 ppm), RBC (50 ppm) and brain (50 ppm) cholinesterase depression as the only sign of toxicity.

Core Classification - Supplementary

(Lacks histopathology report)

Materials and Methods

The material used in this study was technical Bidrin, a dark brown liquid, 80 parts (by weight) 3-(dimethoxyphinyloxy)-N,N-dimethyl-cis-crotonamide.

Thirty-two beagle dogs, equally dividied by sex and ranging in age from 106 to 117 days, were used for this study. After 6 weeks of feeding on the control diet the animals were distributed into 4 groups, each consisting of 4 males and 4 females. The groups were fed diet containing 0, 1.0, 5.0 and 50.0 ppm Bidrin for 13 weeks. The dogs were weighed individually at weekly intervals. Food intake was determined daily.

Blood samples were taken from each dog initially and at intervals of 5, 7, 10 and 13 weeks. LDA, serum protein, hemaglobin, hematocrit, and WBC determinations were performed. Plasma and RBC cholinesterase activity was assayed. Urine samples (three from each animal) were analyzed for albumin, sugar, specific gravity and pH and examined microscopically.

Terminally, the animals were killed, their viscera were examined for gross pathological changes, and sections of the viscera were prepared for microscopic examination. The liver, heart, lungs, kidneys, spleen, brain, gonads, pituitary, adrenals and thyroids were weighed individually. Portions of each brain were frozen for analysis of cholinesterase.

Reported

1. All of the dogs survived without exhibiting any signs of illness.

2. Bidrin Insecticide in the diets of the dogs in the concentratons specified, had no effect on their eating habits, and did not alter their rate of growth.

3. The compound had no effect on the content of hemoglobin, the volume of the erythrocytes, the relative numbers of the leukocytes, the protein content of the serum, or the lactic dehydrogenase in the blood of the dogs.

4. There were no pathological alterations in the major organs of the dogs.

5. There was marked inhibition of the activity of the cholinesterase in the brain, erythrocytes, and the plasma of the dogs that were fed on diets containing Bidrin Insecticide in the concentration of 50.0 parts per million. There was only a temporary inhibition of moderate degree in the activity of the cholinesterase in the plasma of the dogs that were fed on the diet containing 5.0 parts per million, and a still lesser degree of inhibition in the plasma of those that were fed on the diet containing 1.0 part per million;

Discussion

In general, this study filled Core Guidelines, however the report lacked a histopathology report and therefore must be classified as supplementary. Provision of this report would probably improve the classification to Core. A NOEL of 5 ppm was demonstrated on brain and RBC cholinesterase inhibition. A NOEL may be present at 1 ppm for plasma cholinesterase.

MIRD 00013569

Chemical

Bidrin

Dichlorovos (Vapona)

Mevinphos (Phosdrin)

Ciodrin

Chlorfenvirphos (birlane)

SD 779 (dimethex, analogue of Ciodrin)

Daraoxon

Type of Formulation

Bidrin	Technical
Dichlorovos	Technical
Mevinphos	Technical
Ciodrin	Technical
Chlorfenviphos	Technical
SD 7779	Technical
Daroxon	Technical

Citation

Reiff, B. (1968) Pharmacological Studies into the Toxic Actions of Cholinesterase Inhibitors: 7. The Effect of Antidotes on the Subcutaneous Toxicity of Some Organophosphate Insecticides in the Rat: Group Research Report TLGR. 0030.68. (Unpublished study received June 2, 1971 under 1F1062; prepared by Tunstall Laboratory in cooperation with Wocostock Agricultural Research Center, submitted by Shell Chemical Co., Wash., D.C.; CDL:091826-R).

Reviewed by - Robert P. Zendzian, Ph.D. 11/5/87

TOPIC

This study has information pertinent to the discipline toxicology, topic antidoting acute toxicity. It does not relate to any requirements in the proposed Guidelines data requirements.

Conclusion

Treatment of experimental organophosphate poisoning in the rat was most effective using a combination of atropine sulfate and the oximes P2S or Toxogonin. The combination with Toxogonin was the most effective combination.

Core Classification - Not Applicable

Materials and Methods

All materials were administered to female rats (CF strain, bred under S.P.F. conditions, weight range 200-250 g, age range 12-13 weeks) by subcutaneous injection.

The organophosphorus compounds included in this investigation were:

Dimethoxy vinyl phosphates	
Bidrin	86.8% alpha-isomer, CIBA
Dichlorvos (Vapona)	94.0% A.M., Modesto
Mevinphos (Phosdrin)	98.6% A.M., Shell Berre
Ciodrin	86.0% A.M., Modesto
Diethoxy vinal phosphates	
Chlorfenvinphos (Birlane)	92.0% A.M., Woodstock A.R.C.
SD 7779	diethoxy analogue of Ciodrin, 99.0% A.M., Modesto
and a reference organophosphate	
Paraoxon	99.9% A.M., Baywood Chemicals Co.
Antidotes	
Atropine methonitrate, B.P.	Burroughs Wellcome, London
Atropine sulphate, B.P.	John Bell, Hills and Lucas Ltd., London
Oximes	
P2S (2-hydroxy-iminomethy)-N-methylpyridinium methane-sulphenate)	Koch-Light Laboratories, Colnbrook, Bucks.
Toxogonin (Bis-(4-hydroxy-iminomethylpyridinium (1)-methyl)-either chloride	Merck & Co., Darmstadt, Germany

The organophosphorus compounds were given in logarithmically increasing doses with constant amounts of antidotes.

Groups of five animals were injected identically with:

1. Organophosphate without antidote.
2. Organophosphate with atropine methonitrate 18.02 mg/kg.
3. Organophosphate with atropine sulphate 17.40 mg/kg.
4. Organophosphate with P2S 50 mg/kg.
5. Organophosphate with atropine sulphate 17.40 mg/kg and P2S 50 mg/kg.
6. Organophosphate with Toxogonin 90 mg/kg.
7. Organophosphate with atropine sulphate 17.40 mg/kg and Toxogonin 90 mg/kg.

Deaths were recorded for 7 days at 24-hour intervals. Final mortality results were expressed as a percentage of animals treated in each group.

Reported

The results of this study are summarized in the following tables from the report.

Table 1 - The Subcutaneous LD_{50} Values of Some Organophosphate Insecticides to Female Rats with and without the Administration of Antidotes

Compound	LD_{50} values in mg/kg body weight calculated as active insecticidal material*						
	Bidrin	Dichlorvos	Mevinphos	Ciodrin	Chlorfenvinphos	SD 7779	Paraoxon
Untreated	8.1 (6.7-9.6)	11.6 (9.8-13.6)	1.2 (1.1-1.3)	46.8 (39.1-56.4)	15.6 (12.4-19.2)	3.9 (3.3-4.6)	0.4 (not obtained)
Atropine methonitrate 18.02 mg/kg s.c.	18.7 (17.6-19.7)	14.2 (12.0-16.8)	1.3 (1.1-1.5)	70.2 (60.2-81.6)	22.2 (15.5-29.5)	8.8 (7.5-10.5)	0.4 (not obtained)
Atropine sulphate 17.40 mg/kg s.c.	59.5 (53.4-65.2)	39.0 (32.7-47.5)	1.9 (1.6-2.2)	93.7 (80.6-108.9)	37.4 (29.6-47.4)	15.8 (13.7-18.2)	0.8 (0.7-1.0)
P2S 50 mg/kg s.c.	22.2 (18.9-26.4)	56.2 (41.6-78.8)	2.1 (1.7-2.7)	75.2 (64.1-89.7)	19.4 (16.0-23.5)	13.6 (11.8-15.7)	0.8 (0.7-1.1)
Atropine sulphate 17.40 mg/kg s.c. and P2S 50 mg/kg s.c.	59.3 (48.7-70.8)	207.7 (143.3-311.8)	2.3 (2.0-2.7)	87.6 (75.0-101.1)	77.7 (61.2-98.5)	20.9 (19.2-22.7)	1.6 (1.4-1.8
Toxogonin 90 mg/kg s.c.	33.7 (26.9-41.8)	79.4 (57.4-109.8)	2.4 (2.0-2.8)	65.0 (53.5-76.9)	35.4 (26.2-36.6)	32.7 (28.3-36.6)	2.5 (not obtained)
Atropine sulphate 17.40 mg/kg s.c. and Toxogonin 90 mg/kg s.c.	82.0 (69.8-96.1)	267.8 (191.4-374.8)	5.3 (4.9-6.1)	80.3 (72.3-90.3)	287.9 (241.1-347.2)	50.5 (42.8-60.0)	72.0 (61.6-86.2)

*Figures in parentheses denote 95% confidence limits.

The relative effectiveness of the treatments is shown in the following table. Combination of atropine sulfate with either P25 or with Toxogin (most effective combination) is more effective than any agent alone.

Table 3 - Multiples of the LD_{50} of Organophosphate Insecticides After Administration of Antidotes. The figures indicate the ratio of LD_{50} s.c. after antidote treatment over the untreated LD_{50} s.c.

Compound	Bidrin	Dichlorvos	Mevinphos	Ciodrin	Chlorfenvinphos	SD 7779	Paraoxon
Untreated	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Atropine methonitrate 18.02 mg/kg s.c.	2.3	1.2	1.1	1.5	1.4	2.3	1.0
Atropine Sulphate 17.40 mg/kg s.c.	7.3	3.4	1.6	2.0	2.4	4.1	2.0
P25 50 mg/kg s.c.	2.7	4.8	1.75	1.6	1.2	3.5	2.0
Atropine Sulphate 17.40 mg/kg s.c. and P25 50 mg/kg s.c.	7.3	17.9	1.9	1.9	5.0	5.4	4.0
Toxogon 90 mg/kg s.c.	4.2	6.8	2.0	1.4	2.3	8.4	6.2
Atropine Sulphate 17.40 mg/kg s.c. Toxogon 90 mg/kg s.c.	10.1	23.1	4.4	1.7	18.5	12.9	180.7

Discussion

This is an extensive report of a well designed study. Only that portion directly dealing with antidotal activity has been extracted.

MRID 0001345

Chemical - Bidrin

Type of Formulation - Radio labeled 95% cis isomer

Citation

Poonawalla, N.H. (1965) Excretion, Distribution, and Metabolism of Bidrin-(R)-Insecticide (SD 3562) after Oral and Intravenous Administration to Rats: Technical Report No. M-14-65. (Unpublished study received January 28, 1966, under 201-142; submitted by Shell Chemical Co., Washington, D.C.; CDI:000834-R.)

Reviewed by - Robert P. Zendzian, Ph.D. 12/9/81

Topic - This study has information pertinent to the discipline toxicology topic metabolism. It relates to the proposed Guidelines data requirements 163.85-1.

Conclusion:

In the male rat, Bidrin is rapidly excreted in urine mainly in the dimethyl and other hydrophilic phosphides and the de N-methylated Bidrin. The compound and its metabolites do not accumulate in tissue. Studies are needed in the female rat.

Core Classification - Minimal (males only). Females required.

Materials and Methods

14C labeled Bidrin of a specific activity of 1.2 mc/mM was used for this study. The label was a carbon of methoxy group. The compound was 99% radio chemically pure and consisted of 95% cis isomer. The compound was prepared in corn oil so that each milliliter contained 2.07 mg of 14^C Bidrin equivalent to 10.2 uC.

1. Two young male rats received one milliliter of the corn oil solution orally and were placed in metabolism cages. Urine and feces were collected separately at 6, 24, 48 and 92 hours after dosing. Urine was analyzed for total radio activity, dimethyl and other hydrophilic phosphides, de N-methylated Bidrin and unchanged Bidrin. Feces were ground and extracted with acetone, and analyzed for Bidrin.

2. One young healthy male rat received one milliliter of the corn oil solution orally. After six hours, the animal was sacrificed and all tissues separated and extracted with acetone. The extract was analyzed for Bidrin and metabolites as noted in Part 1.

3. One young healthy male rat received 1.25 uc of Bidrin in 50% alcoholic solution intravenously. The animal was then treated as in Part 2.

Reported

1. Results of oral dosing two male rats are summarized in the table taken from the report.

Table 1. EXCRETION OF BIDRIN AND ITS METABOLITES IN URINE BY RATS AFTER ORAL ADMINISTRATION

Hours	6				24				48				92		Total Excretion
	A	B			A	B			A	B			A	B	
		x	y	z		x	y	z		x	y	z		x	
Rat 1	53.5	50	40	5	17.3	65	30	<1	3.1	>95	-	-	0.2	100	72.1%
Rat 2	46.2	60	30	3	19.8	65	30	<1	3.1	>95	-	-	1.2	100	70.3%

A = % of administered Bidrin.
B = Analysis of the excretary products.
x = % of compound excreted as dimethyl and other hydrophilic phosphates.
y = % of compound excreted as de N=methylated Bidrin.
z = % of unchanged Bidrin.

Less than one percent of the dose was excreted in the feces.

2. Tissue distribution of Bidrin and its metabolites in one oral dosed male rat are shown in the table taken from the report.

Table 2. EXCRETION AND DISTRIBUTION OF C14 BIDRIN AND ITS METABOLITES AFTER ORAL ADMINISTRATION

	A	B	C	D	E	F
Stomach with duodenum	1.2	32×10^6	1.60	0	50	50
Contents of stomach	1.81	33.1×10^5	24.80	0	100	0
Gut	7.10	21.7×10^5	0.64	0	70	30
Contents of gut	2.79	9.3×10^3	0.11	0	100	--
Kidneys	1.36	18.4×10^3	0.10	5	90	5
Liver	5.58	10.7×10^3	0.25	5	90	5
Spleen	0.36	5.5×10^3	<0.01	--	--	--
Testes	1.39	2.9×10^3	0.01	--	--	--
Heart	0.63	14.9×10^3	0.03	0	95	5
Lungs	0.84	2.8×10^3	<0.01	--	--	--
Brain	1.80	3.4×10^3	0.02	--	--	--
Blood	4.54	4.4×10^3	0.08	5	92	3
Thymes	0.51	6.6×10^3	0.01	--	--	--
Skin and Subcutaneous fat	26.47	88.6×10^3	9.70	75	20	5
Muscles, bones, abdominal fat	107.84	8.7×10^3	3.87	15	75	10
Urine	2.08	40.8×10^5	35.12	15	75	10
Feces	2.42	4.1×10^3	0.04	--	--	--

A = Wt. of tissue in g
B = d.p.m. per g of the tissue
11220 d.p.m. is 1 p.p.m.
C = % of administered activity
D = % of unchanged Bidrin
E = % of dimethyl phosphate and more hydrophilic compounds
F = % of other metabolites

3. Tissue distribution of Bidrin and its metabolites in the intravenously dosed male rat are shown in the table taken from the report.

Table 3. EXCRETION AND DISTRIBUTION OF C14
BIDRIN AND ITS METABOLITES AFTER INTRAVENOUS ADMINISTRATION

	A	B	C	D	E	F
Stomach with duodenum	2.30	2,950	0.24	0	100	0
Gut	6.83	820	0.20	0	100	0
Contents of gut	2.79	700	0.07	0	100	0
Heart	1.30	7,400	0.34	5	80	15
Lungs	1.57	570	0.03	--	--	--
Liver	9.35	650	0.22	5	94	1
Spleen	0.49	1,600	0.03	--	--	--
Brain	1.93	950	0.07	--	--	--
Blood	4.81	4,150	0.72	7	90	3
Kidneys	1.85	4,850	0.32	5	94	1
Tail	5.81	6,900	0.14	50	45	5
Skin with Subcutaneous fat	41.30	--	0.00	--	--	--
Muscles, bones	149.59	800	4.46	5	90	5
Abdominal fat	31.95	--	0.00	--	--	--
Urine	7.99	--	74.18	12	80	8

A = Wt. of tissue in g
B = d.p.m. per g of the tissue, 11220 d.p.m. is 1 p.p.m.
C = % of administered activity
D = % of unchanged Bidrin
E = % of dimethyl phosphate and more hydrophilic compounds
F = % of other metabolites

Discussion:

The study is adequate to assess the metabolism and tissue distribution of Bidrin in male rats, but similar work is required in females to determine if any sex related differences in metabolism exist.

Chemical - Bidrin

Type of Formulation - Technical

Citation

Shellenberger, T.F.; Newell, G.W. (1962) Final Report: Acute and Subacute Toxicity and Cholinesterase Studies of Shell Compound SD 3562: SRI Project No. PB-3797. (Unpublished study including addendum letter report dated April 27, 1962, from T.F. Shellenberger and C.W. Newell to F.F. Feichtmeir, received February 2, 1962, under 201-142; prepared by Stanford Research Institute, submitted by Shell Chemical Co., Washington, D.C.; CDI:000826-A).

Reviewed by - Robert P. Zendzian, Ph.D. 12/3/81

Topic - This study has information pertinent to the discipline toxicity subjects, acute toxicity, subacute toxicity and cholinesterase studies. It relates to the proposed Guideline data requirements 163.81-1, 163.81-2, 163.81-4, and 163.82-2.

Conclusion:

1. Acute Mouse Oral LD_{50} approximately 12.6-15.8 mg/kg
2. Acute Rat, Oral LD_{50} 25 (19-25) mg/kg
3. Rabbit Dermal LD_{50} 224. (102-515) mg/kg

4. Very mild eye irritant

5. Lethal to rats at dietary levels of 750, 2000, and 4000 ppm.

   No effect at 10 ppm.

6. NOEL 12 week feeding rats 15 ppm. No other compound related effect.

7. Rat blood cholinesterase 6 weeks, depressed at 5 ppm and up.

8. Rat cholinesterase 12 weeks.

   NOEL Blood 0.5 ppm

   NOEL Brain 1.5 ppm

9. Blood cholinesterase dogs

   NOEL 0.5 and 1.5 ppm for 3.5 weeks.

Core Classification

1.	Acute Oral Mouse	Supplementary
2.	Acute Oral Rats	Minimum
3.	Actue Dermal Rabbit	Minimum
4.	Eye Irritation Rabbit	Minimum
5.	Feeding Rat 6 Weeks	Supplementary
6.	Feeding Rat 12 Weeks	Supplementary
7.	Cholinesterase Rats 6 Weeks	Supplementary
8.	Cholinesterase Rats 12 Weeks	Supplementary
9.	Cholinesterase Dogs 3.5 Weeks	Supplementary

Materials & Methods

The technical form of Bidrin was used for these studies. The commercial preparation is a brown liquid with a mild ester odor with a density of 1.19 g/cc at 23°C; it is soluble in water, acetone and ethanol but insoluble in kerosene. The technical material consists of two isomers, the most active insecticidal isomer is the ciscrotonamide configuration. The material utilized continued 75% cis isomer.

1. Acute Oral Toxicity Mice

Non-fasted male Swiss Webster mice (19-21g), 10 animals per dose level, were utilized. Peanut oil was used as a vehicle. Animals were observed closely for 8 hours and then daily for 14 days. Doses of 10, 12.6, 15.8 and 19.9 mg/kg were used.

2. Acute Oral Toxicity Rats

Non-fasted male Long-Evans strain rats (95-110gm), 10 animals per dose, were utilized, peanut oil was used as a vehicle. Animals were observed closely for 8 hours and then daily for 14 days. Doses of 15.9, 20.6, 25.0 and 31.8 mg/kg were used.

3. Toxicity Rabbits

Toxicity was determined in adult albino rabbits (3 per group) weighing 1800 to 2300 grams. An area of back skin was clipped and 24 hours later

undiluted compound was applied at the required dose. The treated area was wrapped with a rubber dam and a towel. The wrapping was removed and the test area washed free of compound after six hours. The animals were observed for six weeks. Doses of 100, 200, 400 and 890 mg/kg were used.

4. Eye Irritation in Rabbits

Small quantities of the technical material (0.1 ml) were placed in the left eye of each of six rabbits. The right eye was untreated and served as a control. The method of Driaze was used in evaluation of the effects on the eyes.

5. Two-week Feeding Rats

The compound was fed to groups of 12 young adult Long-Evans strain rats (6 males and 6 females in each group) at dietary levels of 0, 10, 300, 100, 250, 750, 2000 and 4000 ppm. Compound was dissolved in corn oil and added in appropriate amount to the feed. Fresh diet, mixed weekly, was refrigerated until fed. Stability tests were performed. Animals were weighted weekly. Plasma and RBC cholinesterase activity was determined on 3 males and 3 females from each group surviving two weeks.

6. 12-week Feeding Rats

After a 2-week preconditioning period, 96 young adult Long-Evans strain rats were randomized into 4 groups (12 males and 12 females) per group, housed 4 per cage and fed doses containing 0, 15, 45, and 135 ppm Bidrin

for 12 weeks. Each animal was weighed at the start of the experiment and weekly thereafter. Hematocrit, hemiglobin, RBC, WBC and different counts were performed on 2 males and 2 females from each group before and at 4-week intervals during the study.

The animals were sacrificed at two weeks and examined for gross pathology. Liver, kidney, spleen, heart and testes or ovary were weighed. Sections of those tissues and lung, adrenal gland, pancreas, stomach, small intestine, prostate or uterus, voluntary muscle, femur, brain, pituitary, submaxillary gland, major sublegenal gland, lymph node, thyroid, parathyroid, harderian gland, laerimal gland and thymus were examined for microscopic pathology.

7. Cholinesterase Studies Rats 6 Weeks

Young adult Long-Evans strain rats were assigned to five groups, 4 males and 4 females each, and fed diets containing 0, 5, 10, 20 and 40 ppm Bidrin. Whole blood cholinesterase levels were determined before treatment and weekly thereafter. During the 4th, 5th and 6th week, one male and female from each group were sacrificed for determination of brain cholinesterase.

8. Cholinesterase Studies Rats 12 Weeks

Weanling Long-Evans strain rats were randomly distributed into 4 groups (30 males and 30 females each) and fed diets containing Bidron 0, 0.5, 1.5 and 4.5 ppm. The animals were weighed weekly. During the 2nd, 4th, 8th

and 12th week, 5 males and 5 females from each group were sacrificed for determination of whole blood and brain cholinesterase. After the 12th week, surviving animals were fed a compound-free diet for three weeks. Cholinesterase analysis was made on 5 males and 5 females from each group at week 13, 3 males and 3 females from each group at week 14, and 2 males and 2 females from each group at week 15.

9. Cholinesterase Studies Dogs 3.5 Weeks.

Twelve young adult beagles were assigned to three groups of 2 males and 2 females each. Compound was fed at 0, 0.5, 1.5 and 4.5 ppm. Blood cholinesterase determinations were carried out before treatment and twice weekly during treatment.

Reported

1. Acute and Toxicity Dose Data from the study are presented in the table. Signs of intoxication included salivation, lacrimation, diarrhea and terminal convulsions.

Vehicle	Dosage (mg/kg)	Mortality	Period of Survival	LD_{50} Value (mg/kg)
		Mice		
Peanut Oil	10.0	0/10		
	12.6	0/10		
	15.8	10/10	13-100 min	15
	19.9	7/10	8-50 min	(14-16)

2. Acute Oral Toxicity Rats

Data from the study are presented in the table. Signs of intoxication included tremors, salivation, lacrimation, diarrhea and terminal convulsions.

Vehicle	Dosage (mg/kg)	Mortality	Period of Survival	LD_{50} Value (mg/kg)
		Rats		
Peanut Oil	15.9	2/10	60 min	
	20.0	4/10	52 min-17 hr	
	25.0	6/10	134 min-17 hr	22
	31.8	10/10	19 min-17 hr	(19-25)[a]

[a] 95% confidence interval

3. Percutaneous Toxicity Rabbits

Data from the study are presented in the table. A few rabbits reacted to the compound during the first six hours, however, tremors, salivation and diarrhea frequently occurred within 24 and 48 hours, followed, at toxic levels, by progressive loss of coordination and general weakness, resulting in collapse, prostration, and death.

Vehicle	Dosage (mg/kg)	Mortality	Period of Survival	LD_{50} Value (mg/kg)
Pure Compound	100	0/3		
	200	1/3	3-4 days	
	400	3/3	1-4 days	224
	800	3/3	2.5 hr - 5 days	(102-505)[a]

[a] 95% confidence interval

4. Eye Irritation Rabbits

Erythema of conjectiva (grades 2-3) appeared within 30 seconds of Bidrin application with mild discharge (grade 1). Miosis was observed 7 to 8 minutes after application. Scattered or diffuse opacity was observed when the eye was washed at one minute. Opacity of grade two was observed when washing was delayed for 5 minutes. All treated eyes appeared normal by 24 hours.

5. Two-week Feeding Rats

All rats fed 750, 2000 and 4000 ppm died within 7 days. All surviving animals at all doses except 10 ppm showed significant decrease in weight gain. RBC, plasma, whole blood and brain cholinesterase activity was substantially inhibited at all dietary levels in both sexes.

6. 12-week Feeding Rats

Weight gain in male rats was significantly depressed at 135 ppm but not at 15 and 45 ppm. In female rats, significant weight depression occurred at 135 ppm and during the first week at 45 ppm. No depression occurred at 15 ppm. No other compound related effects were observed in hematology, gross pathology, or histopathology.

7. Cholinesterase Study Rats 6 Weeks

Cholinesterase depression occurred at all doses tested.

8. Cholinesterase Study Rats 12 Weeks

No effect on growth rate was reported. Whole blood cholinesterase activity was not effected at 0.5 ppm in males and females. Significant depression occurred at 1.5 and 4.5 ppm in both sexes. Brain cholinesterase remained within the normal range at 0.5 ppm for males and females. At 1.5 ppm cholinesterase levels were depressed in both sexes but not significantly. Significant depression occurred at 4.5 ppm in both sexes. Whole blood cholinesterase to normal within two weeks after stopping treatment and brain within three weeks.

9. Cholinesterase Study Dogs 3.5 Weeks

Whole blood cholinesterase was depressed to barely significant values at 4.5 ppm. No effect at 0.5 and 1.5 ppm. RBC cholinesterase was slightly

depressed at 4.5 ppm but not at 0.5 and 1.5 ppm. Plasma cholinesterase was depressed only slightly at 0.5 and 1.5 ppm but somewhat more at 4.5 ppm.

Discussion

1. Mouse LD_{50}

Contrary to the report, the data do not permit calculation of an LD_{50}.

2. Rat LD_{50}

The data indicate tox category I.

3. Percutaneous Toxicity Rabbit

The data indicate tox category I.

4. Eye Irritation Rabbits

The data indicate tox category III.

5. Two-week Feeding Rats

As a preliminary study, the data shows toxicity at doses of 10 ppm and up.

6. Twelve-week Feeding Rats

A NOEL was demonstrated at 15 and 45 ppm in males, and 15 ppm in females (weight gain). Insufficient animals make this study supplementary.

7. Cholinesterase Study Rats 6 Weeks

As a preliminary study, the data showed depression of cholinesterase at doses of 5 ppm and up.

8. Cholinesterase Study Rats 12 Weeks

A NOEL in whole blood cholinesterase was demonstrated of 0.5 ppm for both sexes. A NOEL on brain cholinesterase was demonstrated at 0.5 ppm and perhaps, 1.5 ppm. Recovery in 2-3 weeks was demonstrated.

9. Cholinesterase Study Dogs 3.5 Weeks

A NOEL for whole blood, plasma and RBC was demonstrated at 1.5 ppm.

MRID 00005117

Chemical: Bidrin

Type of Formulation: Technical

Citation:

Doyle, R.L.; Elsea, J.R. (1965) Repeated Application of Technical Bidrin Insecticide and Azodrin to the Skin of Rabbits: P-44. (Unpublished study received April 2, 1970 under 0F0861; prepared by Hill Top Research, Inc., submitted by Shell Chemical Co., Washington, D.C.; CDL:091487-J)

Reviewed By: Robert P. Zendzian, Ph.D. 11/3/87

Topic:

This study has information pertinent to the discipline toxicology, topic subchronic dermal toxicity. It relates to the Proposed Guidelines data requirements 163:82-2.

Conclusion:

21-day subchronic dermal administration of Bidrin at doses of 20 and 40 mg/kg and Azodrin at doses of 36 and 72 mg/kg produced no compound related effects in rabbits.

Core Classification: Supplementary

Materials and Methods:

The test materials were technical Bidrin 90% and technical Azodrin 4.8 lb/gal. Both materials were dark brown liquids. Ninety healthy young adult albino rabbits, 44 males and 46 females were used for the study. Animals were individually caged and fed Purina Prime Rabbit Pellets and water ad libitum.

The rabbits were assigned at random to five groups to be dosed as follows:

Group 1 (Controls) 5 males and 5 females to receive distilled water at a dosage level of 0.6 ml/kg/day.

Group 2 10 males and 10 females to receive a 5.0% volume/volume aqueous solution of Technical Bidrin Insecticide at a dosage level of 0.3 ml/kg/day, equivalent to approximately 20 mg Bidrin/kg/day.

Group 3 10 males and 10 females to receive a 5.0% volume/volume aqueous solution of Technical Bidrin Insecticide at a dosage level of 0.6 ml/kg/day, equivalent to approximately 40 mg Bidrin/kg/day.

Group 4 10 males and 9 females to receive a 1.8% weight/volume aqueous solution of Azodrin, 4.8 lb/gal at a dosage level of 2.0 ml/kg/day, equivalent to 36 mg Azodrin/kg/day.

Group 5 8 males and 12 females to receive a 3.6% weight/volume aqueous solution of Azodrin, 4.8 lb/gal at a dosage level of 2.0 ml/kg/day, equivalent to 72 mg Azodrin/kg/day.

The fur was removed from the abdominal and lateral skin areas initially and periodically thereafter as required, using electric clippers. The abdominal skin area of one-half of the animals in each group was abraded initially and at the beginning of the second and third experimental weeks.

The control and test materials were applied once daily, on a five-day-per-week basis, to the skin of the rabbits for a total of 15 applications. The control and test materials were applied to an area of abdominal skin equivalent to approximately 10% of the total body surface.

Body weights were recorded weekly. Hematology was conducted initially and on the 13th day of the study the dose was introduced under a binder of rubber destal dam secured around the animal's trunk.

Animals were sacrificed after three weeks and a complete gross necropsy was performed. Heart, liver, kidneys, adrenals, spleen and gonads were weighed.

From each abraded skin animal in Group 1, 3 and 5, a microscopic examination was made of a section of skin, heart, liver, kidney, adrenal, spleen, stomach, small intestine, gonads and sternal bone marrow.

Reported:

No significant differences were noted among groups with respect to body weight gains, gross appearance and behavior, food consumption, water consumption, hematological findings or gross or microscopic pathological findings. Two rabbits from the group which received Bidrin at 40 mg/kg/day died. Survival in the remaining groups was 100%.

The majority of the animals showed no gross signs of dermal irritation. A few animals from the control and each test group showed very mild skin irritation characterized by slight erythema (generally confined to abraded-skin animals) and/or slight atonia. Atonia was noted slightly more frequently among the animals which received Azodrin at 72 mg/kg/day.

Discussion:

The Guidelines recommends three dose levels for subchronic dermal toxicity studies at which the highest dose should demonstrate toxic effects. Mechanical limits and/or lack of intrinsic dermal toxicity may make it impossible to demonstrate such effects for a particular compound. In this study, significantly higher doses could have been administered. In the case

of Bidrin, utilizing the pure technical liquid (90 percent Bidrin) and 2 ml of fluid would have allowed a maximum dose in the order of 2000 mg/kg. In the case of Azodrin, a dose in the order of 1000 mg/kg could have been administered. Dispite the fact that this study is otherwise acceptable, it must be classified as supplementary because of the failure to include sufficient toxic dose.

MRID 00013443

Chemical: Bidrin

Ciodrin

Type of Formulation:

Bidrin	Technical
Ciodrin	Technical
	XP-557 38.2% Ciodrin

Citation:

Witherup, S.; Pfitzer, E.; Badford, E.P., Jr. (1965) The Toxicity of Ciodrin-(R)° and Bidrin-(R)° Insecticides When Added to the Air Supplied to Rats. (Unpublished study received January 28, 1966 under 201-142; prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-I).

12/9/81

Reviewed By: Robert P. Zendzian, Ph.D.

Topic:

This study has information pertinent to the discipline toxicology topic acute inhalation toxicity. It relates to the proposed guideline data requirements 163.81-3.

Conclusion:

The acute LC_{50} of the technical ciodrin was approximately 0.6 mg/liter. The acute LD_{50} of XP-557 was between 0.94 and 0.78 mg/liter of ciodrin. The acute LC_{50} of technical bidrin was between 0.48 and 0.72 mg/liter. The acute LC_{50} of a 38.2 percent aqueous bidrin solution was greater than 0.86 mg/liter.

Core Classification: Males minimum

Females required

Material and Methods:

Technical Ciodrin insecticide containing methylbenzyl 3-(dimethoxyphosphinyloxy)-cis-crotonate in concentration of 84 percent (by weight) is a straw colored liquid having a specific gravity (60/60°F) of 1.19. It is miscible in xylene, soluble in ethanol and acetone, and immiscible in water (6).

A commercial product (XP-557) contains ciodrin in concentration of 38.2 percent (w/w) and mixed with ingredients which facilitate emulsification of the insecticide with water permitting its use as an aqueous spray.

Technical Bidrin insecticide containing 3-(dimethoxyphosphinyloxy)-N, N-dimethyl-cis-crotonamide in concentration of 79 percent is a dark liquid

having a specific gravity (60/60°F) of 1.22. The product is miscible in water, acetone, ethanol and xylene and is very slightly soluble in kerosene and diesel fuel (7).

Each of the 3 products was employed in its original state; Bidrin insecticide also was diluted with water to provide an aqueous solution containing the compound in concentration of 38.2 percent by weight.

Any one of the 4 preparations was expressed from a motor-powered syringe at a constant rate into a conduit containing a stream of air flowing at a rate of 40 liters per minute; this provides a mixture of vapor and liquid particles which was supplied continuously to rats confined in a hemispherical glass chamber having a volume of 30 liters. The weight of the material dispensed from the syringe, less the amount deposited on the walls of the conduit, was divided by the total volume of air supplied to the animals and the value resulting was accepted as the average concentration of the formulation in the air provided to the animals.

Male rats of the Charles River CD strain ranging from 250 to 350 grams in body weight were confined in the chamber for a single period of time, the duration depending upon the amount of the insecticide dispersed into the air supply. The animals were observed continuously during the period of the exposure and daily during a period of 2 weeks thereafter. The signs of illness were noted and the mortality was recorded.

The results of the Bidrin study were presented by the authors as follows:

Preparation employed	Concentration of Bidrin in the product (% wt)	Length of the period of exposure (min.)	Average concentration in the air supply: Formulation (mg./l.)	Average concentration in the air supply: Bidrin (mg./l.)	Mortality D * E
Technical Bidrin	79	60	0.91	0.72	4 - 5
	79	60	0.61	0.48	0 - 5
Aqueous Bidrin solution	38.2	60	2.20	0.80	1 - 5
	38.2	60	2.12	0.81	0 - 5

The 5 deaths occurred during the one hour period of the respective exposure. Various degrees of illness were evident in increases in the respiratory rate and volume, excessive salivation, defecation, general tremors, convulsions, and terminal coma. Upon removal of the ill animals from the inhalation chamber they generally recovered promptly; no delayed effects developed during the subsequent 2-week period the animals were observed.

Reported:

The results of the ciodrin study were presented by the authors as follows:

Preparation employed	Concentration of Ciodrin in the product (% wt)	Length of the period of exposure (min.)	Average concentration in the air supply: Formulation (mg./l.)	Average concentration in the air supply: Ciodrin (mg./l.)	Mortality D * E
Technical Ciodrin	84	45	1.99	1.67	10 - 10
	84	64	0.80	0.67	2 - 5
	84	120	0.73	0.61	3 - 5
	84	240	0.41	0.34	0 - 5
XP-557	38.2	60	2.47	0.94	7 - 10
	38.2	60	2.04	0.78	0 - 10
	38.2	140	1.10	0.42	0 - 5

*E = Number of rats exposed

D = Number of deaths occurring in the group

During each period of exposure, rats developed some degree of illness, indicated variously by restlessness, increases in the respiratory motions, generalized tremors, salivation, weakness, excessive defecation, convulsions, dyspnea, and terminal coma. After removal of the animals from the inhalation chamber into a fresh atmosphere, they generally recovered promptly; all of the deaths occurred during the specified period of exposure or within 2 hours after the animals had been removed from the chamber.

Discussion:

The study is adequate to assess the acute inhalation toxicity of the compounds in male rats however a similar study in female rats is required.

MRID 00013444

Chemical - Bidrin (Dictrophos)

Type of Formulation - Technical

Citation

Witherup, S.; Stemmer, K.L.; Schlecht, H. (1963) Specific Physiological Effects Bidrin, Vapona, and Ciodrin Insecticides in chickens. (Unpublished study received Jan 28, 1966 under 201-142: prepared by Univ. of Cincinnati, Dept. of Preventive Medicine and Industrial Health, Kettering Laboratory, submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-J)

Reviewed by - Robert P. Zendzian, Ph.D. Pharmacologist

Topic - This study has information pertinent to the discipline toxicology, topics delayed neurotoxicity study (163.81-7) and subchronic neurotoxicity studies (163.82-5).

Conclusion

Single oral doses of up to LD_{50} doses Bidrin (7.4 $\pm$ 0.7 mg/kg), Vapona (22.8 $\pm$ 1.6 mg/kg) and Ciodrin (147 $\pm$ 8 mg/kg) in hens did not produce delayed neurotoxicity. Repetitive dosing of the three pesticides at doses approximately equal to 0.1 of an LD_{50} for three weeks did not produce delayed neurotoxicity.

Core Classification - Minimum

Materials and Methods

Technical Bidrin (79% by weight active), technical Vapona (93% active) and technical Ciodrin (84% - active) were used in this study. Trimethyl phosphate (98 + %) and technical triothocresyl phosphate were used as positive control materials. White Leghorn hens 12 to 18 months of age were dosed orally by gelatin capsule containing measured amounts of the appropriate compound. The following ~~stratic~~ were performed:

Acute oral toxicity of each of the five compounds were determined using the following doses and number of hens.

Bidrin 3 (2), 5 (2), 7 (4), 10 (6) and 16 (6) mg/kg (# hens). Vapona 10 (2) 16 (3), 24 (5), 36 (6) and 55 (4) mg/kg (# hens). Ciodrin 55 (2), 80 (3), 120 (4), 180 (5) and 280 (4) mg/kg (# hens). Trimethyl phosphate 0.28 (2), 0.42 (2), 0.62 (3), 0.94 (3), 1.40 (4) and 2.1 (2) mg/kg (# hens). Tri-o-cresylphosphate 1.4 (1), 2.1 (1) 3.2 (2), 4.7 (1), 7.0 (1) and 10.0 (1) mg/kg (# hens).

Repetitive oral doses of each of the five compounds.

Fifteen hens were dosed with each compound at a dose approximately equivalent to 0.1 of the LD_{50} on each of several days during 2 or 3 weeks as shown in the following schedule.

	Week 1	Week 2	Week 3
Bidrin	1.5 mg/kg x 2	0.75 mg/kg x 5	0.75 mg/kg x 5
Vapona	2.5 mg/kg x 5	2.5 mg/kg x 5	2.5 mg/kg x 5
Ciodrin	58.8 mg/kg x 2	14.7 mg/kg x 5	14.7 mg/kg x 5
Trimethyl phosphate	151 mg/kg x 5	151 mg/kg x 4	None
Tri-o-cresyl phosphate	1.0 gm/kg x 5	1.0 gm/kg x 4	None

All treated hens were observed daily for signs of illness.

Reported

The acute oral LD_{50} of the five compounds were reported as Bidrin 6.4 $\pm$ 0.7, vapona 22.8 $\pm$ 1.6, Ciodrin 147 $\pm$ 8, trimethyl phosphate 755 $\pm$ 16 and tri-o-cresyl phosphate > 10,000 mg/kg. Hens receiving toxic doses of Bidrin, Vapona and Ciodrin showed tremors, unsteadiness in gait, lacrimation, salivation, muscular fasciculation, diarrhea, labored respiration, severe tremors and prostration. Birds either died in 24 hours or recovered.
No specific pathological changes were found in hens that recovered.

Hens given toxic amounts of trimethyl phosphates showed generalized weakness, labored respiration, occasional clonic convulsions, collapse and terminal coma. All deaths occurred within 24 hours after dosing. No specific pathological changes were found in hens that recovered.

Hens given tri-o-cresyl phosphate showed no toxic signs for the first week after dosing. During weeks two and three, the hens given doses of 3.2 or more

gm/kg developed ataxia progressing to paralysis of the legs. Histopathological examination revealed focal demyelination of the sciatic nerve and neurophagia of the cortex of the brain.

Multiple doses.

The doses of Bidrin and Ciodrin during the first week proved too toxic and had to be decreased for the second and third week. Hens receiving Bidrin, Vapona or Ciodrin showed signs of acute toxicity following each dose. The signs were similar to those seen following single acute doses and the hens recovered in 24 hours. No permanent illness was observed. No pathological lesions were found in the hens; the peripheral nerves were normal.

Hens receiving trimethyl phosphate or tri-o-cresyl phosphate exhibited weakness progressing to paralysis. Histopathological damage to the nerve, demyelination of the peripheral nerve, neurophagia of the cerebral cortex were observed in the treated hens.

Discussion

The studies reported do not strictly follow the proposed guidelines for neurotoxicity testing in the hen but are sufficient to establish a lack of neurotoxicoly of the doses tested. Higher doses might here been utilized if the hens were protected from toxicity by atrophiee and 2-PAM. In addition the three pesticides, Bidrin, Vapona and Ciodrin have chemical structures which have not been found to produce delayed neurotoxicity in chickens.

MRID 00012438

Chemical - Bidrin

Type of Formulation - Technical

Citation

Brown, V.K.; Ferrigan, L.W.; Stevenson, D.E. (1964) Technical Memorandum: Toxicological Investigations with Bidrin: Number Tox 31/64. (Unpublished study received Jan 28, 1966 under 201-142; prepared by Shell Research, Ltd., submitted by Shell Chemical Co., Washington, D.C.; CDL:000834-D)

Reviewed by - Robert P. Zendzian, Ph.D. Pharmacologist 12/14/87

Topic - This study has information pertinent to the discipline toxicology topic acute oral and dermal toxicity. It relates to the proposed Guidelines data requirements 16 .81-1, and 163.82-2.

Conclusion

The acute oral toxicity of technical Bidrin and solutions of Bidrin was determined. The acute oral LD_{50} was 12.8-30.2 mg/kg rats, 20-50 mg/kg mice, 2.5-5 mg/kg ducks and 5-22.5 mg/kg chickens. The percutaneous toxicity of Bidrin, in various solvents, on rats ranged from 35-286 mg/kg. Atropine was an effective antidote of Bidrin toxicity.

Core Classification - Supplementary

Materials and Methods

Technical Bidrin (90% w/v) was utilized in this study. The following procedures were reported:

Rats 15-25 gm, 4 males, and 4 females per dose were fasted overnight. Doses of Bidrin 7.9, 12.6, 15.8, 20, 25, 31.8 and 40 mg/kg were administered orally. Doses of Bidrin 25% w/v in isopropyl alcohol or DMSO of 15.8, 20, 25, 31.8, 40, 50, 63 and 80 mg/kg were administered orally. Animals were observed for 10 days.

Mice: Carworth Farms No. 1 mice were utilized. Two males and two females per dose received Bidrin 25% w/v in isopropyl alcohol at doses of 10, 16, 25 and 40 mg/kg orally. Five males and five females per dose received Bidrin 1% w/v in DMSO at doses of 10, 16, 25, 40 and 63 mg/kg orally.

Fowl: Khaki Campbell Ducks were fasted overnight and dosed orally with technical Bidrin in gelatin capsules at doses of 2.5 (2 birds), 5.0 (4 birds) and 7.5 mg/kg (2 birds).

White leghorn chickens were fasted overnight and dosed orally with technical Bidrin in gelatin capsules at doses of 7.5 (4 birds), 10 (4 birds) 12.5 (4 birds) and 15 (4 birds) mg/kg. Equal numbers of males and females were used for each species at each dose.

Acute percutaneous toxicity:

Hooded Lister Rats, 150-250 gm, were utilized. The dorsal neck region was shaved 24 hours before dosing. The test material was applied to the neck region. The animals were individual caged for 24 hours and then washed with water and group caged. The number of rats per dose and the doses utilized were not reported. LD_{50}'s were determined for Bidrin in the form of Technical Bidrin, 10% aqueous solution, 10% isopropanol solution, 24% isopropanol solution, 10% in aqueous dilation of isopropanol solution, 24% isopropyl oxitol solution, 9.2% dimethylsul phoxide solution, 9.2% dimethylsulphoxide and water solution, 9.2% cotton seed oil solution, 9.2% water solution, 9.2% xylene solution and 9.2% methyl salicylate solution.

Antidotal studies in Guinea pigs:

Adult Guinea pigs 1 male and 1 female per dose were dosed subcutaneously with technical Bidrin at doses at 0.030, 0.032, 0.032 and 0.040 m/kg and the LD_{50} determined. Then five males and five females were dosed subcutaneously with 0.2 ml/kg technical Bidrin. Four males and five females were treated with atropine sulphate 17.4 mg/kg followed by Technical Bidrin 0.2 ml/kg or 0.4 ml/kg. Five males and five females were treated with atropine 17.4 mg/kg and P-25 (2-hydroxyiminomethyl N-methyl pyridinium methane sulphorate) 50 mg/kg followed by technical Bidrin 0.2 ml/kg or 0.4 ml/kg.

Reported - Rats (male and female combined) oral

	Technical Bidrin	Bidrin 24% m/v Isopropal Alc	Bidrin 24% m/v Dimethylsulphoxide
LD_{50} mg/kg	12.8	38.7*	30.2*
95% Confidence Limits	9.1-15.7	23.2-34.1	24.7-36.9

* as Bidrin

Mice (male and female combined) oral:

Approximate LD_{50} Bidrin 2% m/v isopropyl alcohol 20 mg/kg.

Approximate LD_{50} Bidrin 1% m/v dimethylsulfoxide 40-50 mg/kg.

Fowl

Technical Bidrin

Khai Campbell ducks (males and females combined) oral, approximate LD_{50} 2.5-5.0 mg/kg.

White leghorn chickens (male and female combined) oral, approximate LD_{50} 10-12.5 mg/kg.

Acute Percutaneous Toxicity

The acute percutaneous toxicity of various Bidrin formulations in Hooded Lister Rats is given in the table.

Test Materials		Male		Female		
	Concentration of Bidrin (calculated at "Pure" Bidrin)	LD_{50} mg/kg	95% Confidence Limits	LD_{40} mg/kg	95% Confidence Limits	Significance of Differential Between Sexes
Undiluted Technical Bidrin (FC 1313	--	136	88-212	111	77-162	11.8
Aqueous Dilution of E.C. (2336/C)	10%	93	55-160	51	35-73	P = <0.01
Isopropanol Solution	10%	190	144-252	82	52-126	P = <0.01
Isopropanol Solution (EF2350)	24%	87	61-125	59	37-92	N.S.
Aqueous Dilution of Isopropanol Formulation (2147/0) (Water:IPA equal parts)	10%	286	161-520	147	105-202	P = <0.01
Isopropyl Oxitol Solution (EF 2350)	24%	67	44-101	59	37-92	N.S.
Solution in Dimethyl-Sulphoxide	9.2%	130	93-210	72	49-105	P = <0.05
Solution in Dimethyl-Sulphoxide and Water (equal parts)	9.2%	125	81-196	63	42-95	P = <0.01
Solution in Cottonseed Oil	9.2%	47	28-79	46	26-78	N.S.
Solution in Water	9.2%	129	87-190	191	117-321	N.S.
Solution in Xylene	9.2%	46	26-78	53	33-85	N.S.
Solution Methyl Salicylate	9.2%	40	20-56	35	24-51	N.S.

N.S. = Not Significant

Antidotal Studies in Guinea Pigs

The acute subcutanious LD_{50} of Bidrin in guinea pigs (male and female combined) was approximately 0.04 ml/kg.

Antidotal treatment produced the results presented below:

	Technical Bidrin 0.2 ml/kg ($5 \times LD_{50}$)			Technical Bidrin 0.4 ml/kg ($10 \times LD_{50}$)		
	M	F	Total	M	F	Total
None	5/5	5/5	10/10	Not Totaled		
Atropine Sulfate (17.4 mg/kg)	0/4	1/5	1/9	3/4	4/5	7/9
Atropine Sulfate (17.4 mg/kg) and P-25 50 mg/kg	0/5	0/5	0/10	0/5	1/5	1/10

Discussion

At best, this study can be considered preliminary. Insufficient animals were used per dose and in many cases the sexes were combined to determine an LD_{50}. In the antidotal study the number of animals and doses utilized was not reported.

END